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Highlights

- This multicentre study included 1,969 COVID-19 hospitalized patients.
- A higher number of onset symptoms was associated with more post-COVID symptoms
- Dyspnea and headache symptoms at onset are associated with post-COVID symptoms.

Short Communication

Symptoms Experienced at the Acute Phase of SARS-CoV-2 Infection as Risk Factor of Long-term Post-COVID Symptoms: The LONG-COVID-EXP-CM Multicenter Study

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Abstract

Objective: This multicenter study investigated clinical risk factors associated with the number of long-term post-COVID symptoms.

Methods: Clinical features, symptoms at hospital admission, hospitalization data, and the number of post-COVID symptoms was systematically assessed from patients recovered from COVID-19 at four hospitals in Madrid (Spain) from February 20 to May 31, 2020.

Results: Overall, 1,969 patients (46.5% women, age: 61, SD: 16 years) were randomly assessed at 8.4 months (SD 1.5) after hospital discharge. Female gender (OR1.82, 95%CI 1.57-2.10), number of morbidities (OR1.182, 95%CI 1.08-1.29), number of symptoms at hospital admission (OR1.309, 95%CI 1.15-1.49) and days at the hospital (OR1.01, 95%CI 1.007-1.017) were associated (all, P<0.001) with more long-term post-COVID symptoms. Further, vomiting (OR1.78, 95%CI 1.26-2.52), throat pain (OR1.36, 95%CI 1.02-1.81), diarrhoea (OR1.51, 95%CI 1.25-1.82), dyspnea (OR1.20, 95%CI 1.01-1.41), or headache (OR1.50, 95%CI 1.28-1.75) as symptoms at hospital admission were also associated (all, P<0.01) with a higher number of post-COVID symptoms.

Conclusion: This multicenter study found that a higher number of symptoms at hospital admission was the most relevant risk factor for developing more post-COVID symptoms, supporting the assumption that a higher symptom load at the acute phase is associated with a greater likelihood of long-term post-COVID symptoms.

Key words: COVID-19, persistent, symptoms, risk factors, acute phase.

Introduction

The presence of post-COVID symptoms ranges from 35% to 60% (Fernández-de-las-Peñas et al., 2021). Identification of risk factors is needed for an early monitoring of individuals at a high risk of developing post-COVID symptoms, yet current data is still limited (Iqbal et al., 2021). Potential identified risk factors described in former literature include female sex, more onset-symptoms (higher symptom load), older age, longer hospital stance, and higher number of comorbidities (Yong et al., 2021). Nevertheless, contradictory results are also observed between studies. Further, most of studies included samples of <300 patients and recruited from single centers (Iqbal et al., 2021). A study including a large number of COVID-19 patients reported a prevalence of long-term sick leave from work of 5.8% (Jacobs et al., 2021). These authors found that female, older age and co-morbid medical conditions were significantly associated with long-term sick leave (Jacobs et al., 2021). We describe here a large multicenter study investigating clinical risk factors related with hospitalized associated with the number of long-term post-COVID symptoms in a large population sample.

Methods

The LONG-COVID-EXP-CM is a multicenter cohort study including individuals hospitalized with a diagnosis of SARS-CoV-2 during the first wave of the pandemic in five public hospitals in Madrid (Spain). A sample of 400 individuals from each hospital was randomly selected. All Local Ethics Committees approved the study (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092-20, HUF/EC1517). Informed consent was obtained from all participants. Participants were scheduled for a telephone interview conducted by experienced healthcare professionals, were systematically asked about a list of post-COVID symptoms (multiple symptoms could be selected by the

same patient), but were free to report any additional symptom that they experienced at the time of study. Clinical data (i.e., gender, age, height, weight, comorbidities), COVID-19 symptoms at hospital admission and hospitalization (i.e., days at hospital, intensive care unit admission) data were collected from medical records.

Mean and standard deviation (SD) or percentages were calculated. Missing values were imputed using median imputation. Multivariate logistic regressions were conducted to analyze associations between clinical and hospitalization variables with the number of post-COVID symptoms (dependent variable) using Python's library statsmodels 0.11.1. Adjusted odds ratio (OR) and confidence intervals (95%CI) were calculated.

Results

From 2,000 patients randomly selected and invited to participate, a total of 1,969 (46.5% women, age: 61, SD: 16 years) participated. The most prevalent symptoms at hospital admission were fever (74.6%), dyspnea (31.5%), and myalgia (30.7%). Almost 57.5% of the individuals (n=1,133) reported at least one comorbidity. Participants were assessed 8.4 months (SD 1.5) after hospital discharge. Almost one out of five patients (n=367, 18.7%) were free of post-COVID symptoms, whereas 34.4% (n=679) experienced ≥3 post-COVID symptoms. The mean number of post-COVID symptoms was 1.9 (SD 1.4). The most frequent long-term post-COVID symptoms included fatigue (61.3%) and dyspnea (23.3%).

Female gender (OR1.82, 95%CI 1.57-2.10), number of COVID-19 symptoms at hospital admission (OR1.309, 95%CI 1.15-1.49), number of pre-existing medical co-morbidities (OR1.182, 95%CI 1.08-1.29), and days at hospital (OR1.01, 95%CI 1.007-1.017) were independently associated (all, P<0.001) with more long-term post-COVID

symptoms: the higher the number of COVID-19 onset symptoms or the higher the number of co-morbidities, the higher the number of post-COVID symptoms (**Figure**). No specific co-morbidity (e.g., obesity, hypertension) was associated with a greater number of post-COVID symptoms. Some specific symptoms at the acute phase were also independently associated (all, P<0.01) with a higher number of long-term post-COVID symptoms (**Table**): vomiting (OR1.78, 95%CI 1.26-2.52), throat pain (OR1.36, 95%CI 1.02-1.81), diarrhoea (OR1.51, 95%CI 1.25-1.82), dyspnea (OR1.20, 95%CI 1.01-1.41), or headache (OR1.50, 95%CI 1.28-1.75).

Discussion

This multicenter study found that female gender, a greater number of symptoms at hospital admission, a greater number of pre-existing medical co-morbidities, and a longer stance at the hospital were risk factors for developing more long-term post-COVID symptoms. Among all these risk factors, it seems that a higher number of symptoms at hospital admission was the most relevant for developing more post-COVID symptoms. In fact, the presence of some specific symptoms at hospital admission such as vomiting, throat pain, diarrhoea, dyspnea or headache was also associated to long-term post-COVID symptoms. No specific medical co-morbidity was associated with a greater number of long-term post-COVID symptoms. Our data support previous assumptions that a higher symptom load at the acute phase is associated with a greater likelihood of long-term post-COVID symptoms (Iqbal et al., 2021). The role of previous medical co-morbidities as a risk factor for post-COVID symptom needs further studies. We also observed that female gender was a potential risk factor for post-COVID symptoms, in agreement with previous assumptions (Iqbal et al., 2021). Specific studies investigating sex differences are needed.

Our results should be considered according to some potential weaknesses. First of all, only hospitalized patients participated. Second, we did not collect objective data of COVID-19 disease. Third, the cross-sectional design did not permit to determine cause-and-effect associations.

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Author Contributions

Dr Fernández-de-las-Peñas and Dr. Palacios-Ceña had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Dr. Pellicer-Valero. Supervision: Dr. Martín-Guerrero

Declaration of interests

No conflict of interest is declared by any of the authors

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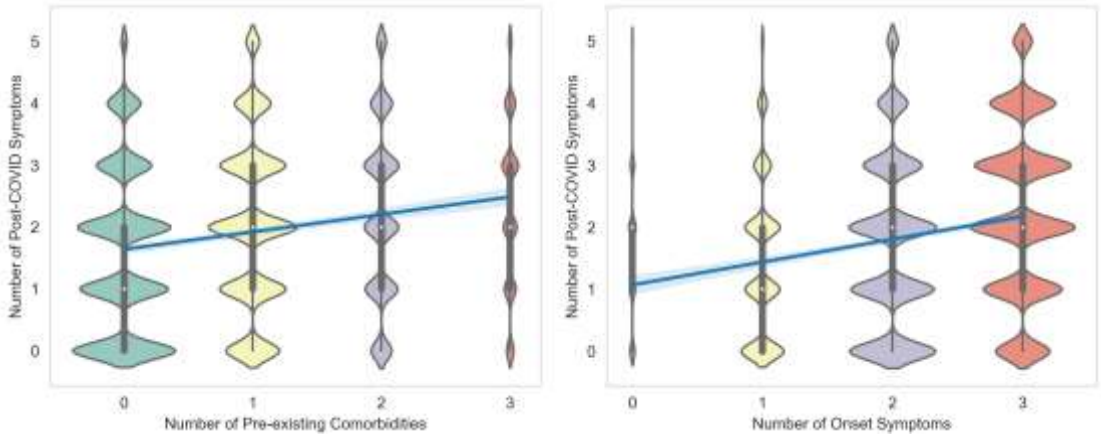

Figure: Positive associations between the number of long-term post-COVID symptoms with the number of pre-existing comorbidities (left) or the number of COVID-19 onset-symptoms at hospital admission

Table: Clinical/Hospitalization Data and Post-COVID Symptoms (n=1,969)

Age, mean (SD), years	61 (16)
Gender, male/female (%)	1,054 (53.5%) / 915 (46.5%)
Weight, mean (SD), kg.	75 (15)
Height, mean (SD), cm.	165 (16.5)
Main Symptoms at hospital admission, n (%)	
Fever	1,469 (74.6%)
Dyspnoea	620 (31.5%)
Myalgia	604 (30.7%)
Cough	549 (27.9%)
Headache	332 (16.9%)
Diarrhoea	210 (10.7%)
Anosmia	167 (8.5%)
Throat Pain	102 (5.2%)
Ageusia	66 (33.5%)
Vomiting	55 (2.8%)
Number of medical co-morbidities, n (%)	
None	836 (42.5%)
One	715 (36.3%)
Two	281 (14.2%)
3 or more	137 (7%)
Medical co-morbidities	
Hypertension	514 (26.1%)
Diabetes	236 (12.0%)
Cardiovascular Disease	234 (11.9%)
Asma	126 (6.4%)
Obesity	88 (4.5%)
Chronic Obstructive Pulmonary Disease	77 (3.9%)
Stroke	38 (2.0%)
Rheumatological Disease	31 (1.6%)
Other (Cancer, Kidney Disease)	332 (16.9%)
Stay at the hospital, mean (SD), days	11.3 (11.4)
Intensive Care Unit (ICU) admission	
Yes/No, n (%)	130 (6.6%) / 1,839 (93.4%)
Number of long-term post-COVID symptoms, n (%)	
None	367 (18.7%)
One	436 (22.1%)
Two	488 (24.8%)
3 or more	679 (34.4%)
Long-Term post-COVID symptoms, n (%)	
Fatigue	1,206 (61.3%)
Dyspnoea	459 (23.3%)
Loss memory	341 (17.3%)
Skin Rashes	236 (12.0%)
Brain fog	189 (9.5%)
Attention Disorders	140 (7.1%)
Palpitations	140 (7.1%)
Gastrointestinal Disorders	133 (6.7%)
Ocular/Vision Disorders	116 (5.9%)
Anosmia	80 (4%)
Ageusia	53 (2.7%)
Throat Pain	50 (2.55%)
Diarrhoea	49 (2.5%)
Voice Problems	39 (2%)
COVID-19 Onset Symptom at Hospital Admission	**Number Long-term Post-COVID Symptoms**
*Dyspnoea (n=620)	2.1 (SD 1.3)
No Dyspnoea (n=1,349)	1.8 (SD 1.4)
*Headache (n=332)	2.2 (SD 1.4)
No Headache (n=1,637)	1.8 (SD 1.3)
*Diarrhoea (n=210)	2.25 (SD 1.4)
No Diarrhoea (n=1,759)	1.8 (SD 1.4)
*Throat Pain (n=102)	2.35 (SD 1.4)
No Throat Pain (n=1,867)	1.85 (SD 1.4)
*Vomiting (n=55)	2.5 (SD 1.4)
No Vomiting (n=1,914)	1.85 (SD 1.3)

* Significant association in the multivariate analysis